IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Jeffrey Olson et al.	Art Unit	: 1637
Serial No.	: 09/697,028	Examiner	: Suryaprabha Chunduru
Filed	: October 25, 2000	Conf. No.	: 3430
Title	: METHODS FOR GENETIC ANALYSIS OF DNA TO DETECT SEQUENCE VARIANCES		

Mail Stop Appeal Brief - Patents
Commissioner for Patents
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REPLY BRIEF

Pursuant to 37 C.F.R. § 41.41, Applicant responds to the Examiner's Answer as follows.

It is Applicant's position that U.S. Patent No. 6,326,145 ("the '145 patent") does not anticipate the claimed invention for at least two reasons. First, the primers disclosed in the '145 patent do not achieve differential amplification of molecules that differ in sequence at a polymorphic site. Second, the primers disclosed in the '145 patent do not include a 5' portion that is incorporated into an amplification product.

There is no evidence that the method of '145 patent achieves differential **amplification**

The Examiner insists, for example at page 5 of the Examiner's Answer, that the '145 patent teaches differential amplification and points to three passages (in columns 10, 12 and 13) supposedly teaching differential application. However, there is nothing in any of these passages of the '145 patent that states or suggests that differential amplification -- as opposed to differential detection -- of two molecules differing at a polymorphic can or is achieved. If differential amplification occurred in any of the methods described by the '145 patent, would not the patent so state? Throughout prosecution and appeal, the Examiner has failed to cite any passage in the '145 patent disclosing differential amplification of two molecules differing at a polymorphic site. The Examiner has pointed to many passages disclosing differential detection of two molecules that differ at a polymorphic site, but this is to be expected because the so-called Scorpion amplification primers produce a fluorescent signal or not depending on whether the

extended primer generated during amplification includes a specific sequence or not. The presence or absence of the specific sequence in the extended primer depends on the sequence present at the polymorphic site of the target molecule. Thus, differential detection, which the '145 patent clearly discloses, does not depend on differential amplification. The '145 patent simply no where states that differential amplification occurs. The Examiner cannot simply assume that it does occur. If the Examiner maintains that differential amplification occurs, Applicant respectfully requests that the Examiner quote the passage in the '145 patent disclosing differential amplification.

Examiner has not to provided any explanation of how the primers described in the '145 patent could achieve differential amplification, as opposed to differential detection. Without a scientifically sound explanation of how differential amplification could occur using the primers of the '145 patent and without a disclosure in the '145 patent that differential amplification does occur, the Examiner is not free to simply assert that differential amplification does occur when the methods of the '145 patent are used.

Example 1 of the '145 patent does **not** use two different alleles

On page 6 of the Examiner's Answer, the Examiner, states that Applicant is incorrect is concluding that Example 1 of the '145 patent does not entail the use of two alleles. As evidence of the presence of two different alleles in Example 1 the Examiner cites column 13, lines 4-8 of the '145. This passage refers to examining the use homozygous (same sequence) alleles and heterozygous (different sequence) alleles. However, this passage is not specific to Example 1. Rather this passage describes various materials that are used in various of the Examples. It is clear that different alleles were used in some of the Examples, but the passage cited by the Examiner does not explain what target molecule was used in Example 1. However, within the description of Example 1, the patent states that the reaction was a homogeneous amplification (Col. 13, line 18). This suggests that only one allele was present. There is certainly nothing in the description of Example 1 to suggest that two alleles where present.

Example 2 amplifies two different alleles and achieves "equally efficient amplification"

In Example 2 the ability of the probes to discriminate between two alleles. Indeed, title of this example is "Allelic Discrimination". The patent states that the same primers and probes were used and that amplification reactions were equally efficient (Col. 13, line 58), but the match sequence was much more readily detected (Col. 13, lines 59-60) was much more readily detected. The Examiner stated (page 7 of the Examiner's Answer) that Applicant is focusing on the probes and not the primers used in Example 2. However, the '145 patent itself states that the primers and probes used in Example 2 were the same as in Example 1. The fact remains, that were two different alleles were used in Example 2, the "amplification reactions were equally efficient.".

<u>The probes described in the '145 patent do not include a 5' portion that is incorporated into an amplification product forming a stem loop</u>

One of the two primers used in the presently claimed methods includes "a 5' portion which, when incorporated into an amplification product, will upon further amplification yield products that form a stable stem-loop structure..." The Scorpion primers of the '145 patent can form a stem-loop, but is very different. Applicant previously argued that the '145 patent does not disclose such an arrangement. The Examiner dismissed this argument as pertaining to Scorpion probes, not the primers involved in amplification, but this is not correct. First, recall that the Scoprion primers include a template binding region and a tail that includes a target binding region (Col. 1, line 57 – col. 2, line 1). The template binding region binds to the template and is extended. The target binding region in the tail will hybridize to a portion of the extension product having the complementary sequence (Col. 2, lines 1-11). This is the stem of the stem loop. However, the target binding region is not incorporated into amplification product because it is not amplified. As the '145 patent explains, when a Scorpion primer is used in an amplification system such as PCR, the Scorpion primer includes a blocking moiety (e.g., hexethylene glycol) that is located between the template binding region and the target binding region that prevents

the target binding region from being amplified. Thus, in column 2 at lines 52-58 the '145 patent describes the primers as follows:

> Conveniently, the novel primer of the invention is used in an amplification system such as the polymerase chain reaction (PCR). In which case the target binding region and the tail region are advantageously arranged such that the tail region remains single stranded, i.e., uncopied. Thus the tail region is nonamplifiable in PCR amplification products…Conveniently, the linker comprises a blocking moiety which prevents polymerase mediated chain extension of the primer template.

Thus, the Scorpion primers do not contain a region that is incorporated into the amplification product and forms a stem-loop structure (when a certain target sequence is present), as required by the present claims. For this second, independent reason, it is clear that the '145 patent cannot anticipate the present claims.

Conclusion

For these reasons and for the reasons stated in the Appeal Brief, Applicant submits that the final rejection should be reversed.

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Respectfully submitted,

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